AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,925	08/14/2001	Peter D Davis	3764-100	2929

7590 04/15/2004

Nixon & Vanderhye
1100 North Glebe Road 8th Floor
Arlington, VA 22201-4714

EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,925	DAVIS ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2 and 4-12* is/are allowed.

6)☒ Claim(s) *13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group 1 is acknowledged, as is the elected specie (the compound recited in claim 12).

Pursuant to the directives of the preliminary amendment filed 1/29/04, claims 1 and 3 have been cancelled, and claims 2, 4, 7, 9 amended. Claims 2 and 4-15 are pending. Claims 2 and 4-12 are characterized as allowable at the present time.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is lacking for therapeutic methods. On page 52 of the specification, it is asserted that the following compound decreased perfused vascular volume by 88% and that the IC_{50} in a tubulin polymerization assay was 58 *micro*molar:

> N-[3-amino-9, l 0, l l-trimethoxy-6,7-dihydro-5H- dibenzo[a,c], cyclohepten-5-yl] acetamide

However, this compound does not fall within the scope of the claimed invention. Even if this compound did fall within the scope of the claimed invention, it would not support claims drawn to a method of treating cancer, or any other therapeutic method.

On page 52 (specification), it is asserted that the compounds of examples 2 and 3 caused a "decrease in vascular volume" as determined by the method of Smith (*British Journal of Cancer* **57**, 247-253, 1988) and of Chalkley (*Journal of the National Cancer Institute* **4**, 47-53, 1943). However, this result does not support claims drawn to a method of treating cancer, or any other therapeutic method. What was shown is a single "snapshot" of vascular volume at a time 24 hours after administration of the compound; the observed decrease in vascular volume could be just a temporary phenomenon with no real impact. Second, there is no indication that there is any selectivity in the vascular damaging effect. If, for example, there is a 70% decrease in vascular volume (70 is the average of 45 and 95) in tumor vasculature, and concomitantly a 50% decrease in vascular volume in other tissues, the result could be that the "cure would be worse than the disease", i.e., an unsustainable degradation of organ function could result, leading to death of the animal. Perhaps the animal can survive 1 or 2 days of the treatment, but if the animal dies as a result of the treatment, the treatment cannot be said to be a therapeutic success. Furthermore, there is no evidence that a 70% decrease in vascular volume will actually reduce tumor volumes.

If the tumors continue to grow and metastasize, but at a slower rate, this would mean that the claimed compound had an effect, but if the animal's condition continues to worsen one cannot say that a successful treatment has been achieved. Further, applicants may be making a "static" assumption about the number of blood vessels present. If the tumor cells secrete additional angiogenesis factor, more blood vessels will grow, and the tumors will grow as well. Applicants may choose to argue that other investigators have achieved therapeutic success with colchicine analogs. In reality, however, structure/activity relationships are "unpredictable". Consider the following:

- As conveyed in Staretz (*J. Org. Chem* **56**, 426, 1991), minor changes in structure can abolish tubulin binding activity. For example, compound 2 (p. 429) was not active (table I, page 430); the structure of this compound is a minor variation of compound 1, which was active.

- Zweig (*J Pharm Exp Ther* **182**, 344, 1972) discloses that minor structural changes in colchicine structure eliminated activity in an assay of rat hindpaw edema.

- Powell (*Medicinal Chemistry Research*, pages 164-173, 1996) discloses that compounds 6 and 7 (table 1) failed to inhibit microtubule polymerization.

- Shi (*Helv Chim Acta* **81**, 1023, 1998) discloses that cholcine analog compounds 6, 7, 12, 15a and 19 failed to inhibit tubulin polymerization. Similar observations were reported in Shi (*J. Org Chem* **63**, 4018, 1998)

- Sterzl (*Folia Microbiol* 27 256, 1982) discloses (table 2) that minor variations in structure of cholchicine eliminated activity in an *in vitro* antibody response assay.

- Boye (*Can J. Chem.* **70**, 1237, 1992) discloses (table 2) that compounds 4, 8, 40, 46, and 47a failed to inhibit tubulin polymerization.

- Zweig (*Biochem. Pharmacol* **22**, 2141, 1973) discloses (p. 2148, col 1, paragraph 1) that colchicoside and colchicosamide both failed to displace ^{3}H colchicine from microtubules.

- Boye (*Med. Chem. Res.* **1**, 142, 1991) discloses (table I) that compounds 3, 5, and 8 inhibited tubulin polymerization to a "negligible" degree.

Thus, where colchicine analogs are concerned, structure/activity relationships are "unpredictable". Accordingly, even if applicants can provide examples of therapeutically effective colchicine analogs falling outside the scope of the claimed invention, the examiner's response will be that one cannot "predict" activity or therapeutic success of one compound based on results obtained with another.

It is suggested that in claim 14 the term "pharmaceutical" be deleted; the term "pharmaceutical" implies an assertion of therapeutic efficacy, which is not in evidence.

Claim 15 is rejected in part because of the recitation of the term "treatment". The following would be one option for claim language:

> *A method of reducing the vascular volume of blood vessels comprising administering to a warm-blooded animal in need thereof an effective amount of a compound according to claim 2*

✧

Claims 13 and 15 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 13, part (d), the following is recited:

  "reaction of a compound of formula II or IV, glycosylation reactions".

  This is a grammatically incomplete phrase. Applicants are requested to explain what is intended here.

- Claim 15 is indefinite as to the nature of the "vascular damaging effect".

- In claim 15, the phrase "such as a human being" fails to set the metes and bounds. It is suggested that this phrase be deleted and that reference to a human be made in a dependent claim.

- In claim 15, the phrase "such treatment" lacks antecedent basis

❄

Reference "HR" was stricken from the IDS because only the abstract was considered. The record should be clear that only the abstract was considered, and not the full document. The following can be listed on another IDS:

English Abstract of Kiselev et a1., "Benzenoid Rearrangement of Colchicine by the Action of Ethylene Glycol" (*Zh. Org. Khim.* **13**(11) 2337-2342, 1977)

The remaining references that were stricken from the IDS were so treated because they were not received.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600